submit that as required by 37 CFR 1.75(d)(1) and MPEP § 608.01(o), the present specification has been amended to recite the specific sections from the '731 patent application which provide support for the amendments to the claims.

Support for the claim amendments and new claim 24 can be found throughout the specification and claims as originally filed. In particular, support for the amendments to claims 1, 3, 17, 18 and 19 can be found in Table 1, beginning on page 13. Support for the amendments to claims 17 and 19 can be found in the paragraph inserted, by the amendments presented herein, at page 10, line 24 of the specification. Support for claim 24 can be found in figure 41,where the location of the residues that are responsible for binding calcium in the EF domains are disclosed, and in the sequence listing as originally filed.

No new matter has been added. Any amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 1-3, 11-12, and 15-23 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-3, 11-12, and 15-23 under 35 U.S.C. § 112, first paragraph because, according to the Examiner, " ***the specification, while being enabling for a method of identifying a compound suitable for treatment wherein the PCIP is 9q***, does not provide enablement for a method of identifying a compound suitable for treatment wherein the polypeptide is a fragment of PCIP 9q." (***Emphasis added***). Specifically, the Examiner states

> Applicant has added the limitation "biologically active" to attempt to better define the function of the fragments of PCIP 9q. There is insufficient guidance as to the nature of the fragments which Applicants claim. There is insufficient guidance provided in the specification as to the relationship between the structure of PCIP 9q and its function.

Applicants respectfully traverse the foregoing rejection for the following reasons. To begin with, the Examiner has admitted that the specification is "enabling for a method of identifying a compound suitable for treatment wherein the PCIP is 9q" (see *supra*). Thus, amended claims 1 and 3, and claims depending therefrom, which are directed to methods which use a 9q polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28 are enabled by Applicants' specification. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, first paragraph rejection as it pertains to the foregoing claims.

With respect to claims 17 and 19, and claims depending therefrom, Applicants submit that, in contrast to the Examiner's assertions, Applicants' specification provides ***ample*** guidance regarding the structure/function relationship of the 9q polypeptides and also provides ***working examples*** which were performed to determine the functional significance of the various domains of the 9q polypeptides (including site directed mutagenesis and deletion mutagenesis). For example, Applicants' specification discloses at page 53, lines 11-14, as well as in Figure 21, that the 9q polypeptides of the invention contain calcium binding domains (EF hands) that are important for the activity of the 9q molecules. In Example 10, Applicants also report that mutations in the three EF hands of PCIPs completely eliminate the effects of PCIPs on Kv4 channel kinetics and conclude that the interaction of PCIPs with Kv4 channels is calcium dependent. As a result, a fragment of a 9q polypeptide comprising a calcium binding domain (an EF hand) (***see claims 20 and 24***) is biologically active and could be used in the claimed methods without any undue experimentation.

In Example 10, Applicants also disclose the generation of N-terminal deletions of the 9q polypeptide. Applicants have demonstrated that deletion of the N-terminal residues (amino acids 2-67) of the human 9q protein did not alter the function of the 9q molecule, *e.g.*, the ability of the molecule to modulate Kv4.2 current amplitude and kinetics (page 49,

line 33 through page 50, line 2 of the specification). Thus, Applicants have demonstrated that the 67 N-terminal amino acid residues of the 9q polypeptide are not critical for the function of this molecule. As a result, a fragment of a 9q polypeptide comprising amino acid residues 68-252 (***see claim 21***) is biologically active and could be used in the claimed methods without any undue experimentation.

In view of the foregoing, Applicants respectfully submit that an ordinarily skilled artisan reading Applicants' specification would have known which fragments of the 9q polypeptide can be used in the claimed methods.

Further, the methods for generating and screening fragments are well known to an ordinary skilled artisan. Moreover, the instant specification describes extensively how to make 9q fragments (see, for example, page 36, line 9 through page 37, line 17) and how to use these fragments in the claimed methods (see, for example, page 32, line 26, through page 33, line 26). The level of skill in the art, as it pertains to the generation and use of polypeptide fragments in screening methods, is such that these experiments are routine and by no means undue.

In view of all of the above, Applicants respectfully submit that an ordinarily skilled artisan reading the foregoing teachings in Applicants' specification would have been able to practice the claimed invention using only routine experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of Claims 1-3, 11-12 and 15-16 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-3, 11-12 and 15-23 under 35 U.S.C. § 112, second paragraph as "being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention." In particular, the Examiner is of the opinion that

> [c]laims 17-23 are indefinite in the recitation of the term "biologically active fragment". The term biologically active is not defined by the claim. Various biological activities can be attributed to a peptide.

Applicants respectfully traverse the foregoing rejection for the following reasons. The term biologically active fragment is an art-recognized term that one of ordinary skill in the art would find to be clear and definite. Further, Applicants define this term in the specification (see the paragraph inserted at page 10, line 24 of the specification). Applicants define "biologically active portion" of a PCIP protein to include, "a fragment of a PCIP protein which participates in an interaction between a PCIP molecule and a non-PCIP molecule." Applicants state that, "typically, biologically active portions comprise a domain or motif with at least one activity of the PCIP protein."

Applicants further define the activities of PCIP molecules as (1) interaction with (e.g., binding to) a potassium channel protein or portion thereof, e.g., a potassium channel comprising a Kv4.3 or Kv4.2 subunit; (2) regulation of the phosphorylation state of a potassium channel protein or portion thereof; (3) association with (e.g., binding to) calcium and acting as a calcium dependent kinase; (4) modulation of a potassium channel mediated activity in a cell (e.g., a cardiac cell such as a pericardial cell, a myocardial cell, or an endocardial cell); (5) modulation of chromatin formation in a cell, e.g., a cardiac cell; (6) modulation of vesicular traffic and protein transport in a cell, e.g., a cardiac cell; (7) modulation of cytokine signaling in a cell, e.g., a cardiac cell; (8) regulation of the association of a potassium channel protein or portion thereof with the cellular cytoskeleton; (9) modulation of cellular proliferation; (10) modulation of the release of neurotransmitters; (11) modulation of membrane excitability; (12) influencing the resting potential of membranes; (13) modulation of wave forms and frequencies of action potentials; and (14) modulation of thresholds of excitation (see page 10, line 24-38 of the specification).

Furthermore, as indicated by the issued claims of more than 1400 United States Patents since 1996 (copies of some of which are submitted herewith as Appendices B-E), the term "biologically active fragments" was well known and understood in the art at the time of the invention. Moreover, the presence of this term in multiple issued claims demonstrates that the term "biologically active fragment" is accepted by the United States Patent and Trademark office as being "clear and definite."

Finally, the Examiner's use of the term "biologically active" when describing the shaker α subunit NAB region (see page 7 of the present Office Action) is further proof of the common use and understanding of this term in the art.

In view of all of the foregoing, the term biologically active is clear and definite and, accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The Examiner further believes that claims 1-3, 11-12, and 15-23 are indefinite over the use of the acronym PCIP.

While in no way acquiescing to the Examiner's rejection, Applicants have amended the claims to define the 9q PCIP polypeptides using sequence identifiers, thereby rendering the foregoing rejection moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of claims 1-3, 11-12, and 15-23 Under 35 U.S.C. § 102

The Examiner has rejected claims 1-3, 11-12, and 15-23 under 35 U.S.C. § 102 as being anticipated by WO 97/31112. The Examiner states that, "[s]ince the Shaker α subunit NAB region protein comprises "fragments" of the PCIP 9q of the present invention, the claims are anticipated."

Applicants respectfully traverse the foregoing rejection for the following reasons.

For a prior art reference to anticipate in terms of 35 U.S.C. § 112 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

As amended, the claims are directed toward methods which use the biologically active fragments of a 9q polypeptide comprising ***at least 10 amino acid residues*** of a sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28. As indicated by the sequence alignment submitted with the Amendment and Response to Office Action on November 9, 2001 as Appendix B, the longest contiguous fragment that the 9q PCIP polypeptide and the Shaker α subunit share is ***four amino acid residues long***. Thus, the WO 97/31112 application does not anticipate the pending claims.

Furthermore, based on the lack of sequence homology that is apparent from the sequence alignment, an ordinary skilled artisan would not expect these proteins to have a

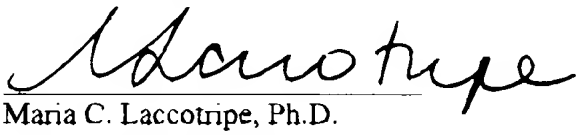
similar function. This is further supported by the fact that these two polypeptides perform different functions *in vivo*. The 9q PCIP is a polypeptide that ***interacts*** with potassium channels and, among other functions, regulate I_{to} current. The Shaker α subunit is the polypeptide that actually ***forms*** a potassium channel. Since the full length polypeptides do not carry out the same function, the small fragments, *i.e.*, four amino acid residues or less, that these two proteins share are unlikely to carry out similar biological functions.

Accordingly, the claims presented herein are not anticipated by WO 97/31112 and Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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Dated: July 12, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1.**(Amended)** A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a 9q PCIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, or a cell expressing ~~the~~said 9q PCIP polypeptide with a test compound; and

b) determining whether said 9q PCIP polypeptide binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

3. **(Amended)** A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a 9q PCIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said 9q PCIP polypeptide, thereby identifying a compound suitable for treating a cardiovascular disorder.

17. **(Amended)** A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a biologically active fragment of a 9q PCIP polypeptide comprising at least 10 amino acid residues of a sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28 or a cell expressing ~~a~~said biologically active fragment of said 9q PCIP polypeptide with a test compound; and

b) determining whether said biologically active fragment binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

18. **(Amended)** The method of claim 17, wherein the binding of said test compound to said biologically active fragment of ~~a~~ said 9q PCIP polypeptide, is detected by a method selected from the group consisting of:

a) detection of binding by direct detection of test compound/biologically active fragment binding;

b) detection of binding using a competition binding assay; and

c) detection of binding using an assay for PCIP activity.

19. **(Amended)** A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a biologically active fragment of a 9q PCIP polypeptide comprising at least 10 amino acid residues of a sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said biologically active fragment of ~~a~~ said 9q PCIP polypeptide, thereby identifying a compound suitable for treating a cardiovascular disorder.

Appendix A

1. A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a 9q PCIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, or a cell expressing said 9q PCIP polypeptide with a test compound; and

b) determining whether said 9q PCIP polypeptide binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

2. The method of claim 1, wherein the binding of said test compound to said 9q PCIP polypeptide, is detected by a method selected from the group consisting of:

a) detection of binding by direct detection of test compound/polypeptide binding;

b) detection of binding using a competition binding assay; and

c) detection of binding using an assay for PCIP activity.

3. A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a 9q PCIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said 9q PCIP polypeptide, thereby identifying a compound suitable for treating a cardiovascular disorder.

11. The method of any one of claims 1, 3, 17 or 19 wherein said cardiovascular disorder is associated with an abnormal I_{to} current.

12. The method of any one of claims 1, 3, 17 or 19, wherein said 9q PCIP is a human 9q.

15. The method of any one of claims 1, 3, 17 or 19, wherein said cardiovascular disorder is long-QT syndrome.

16. The method of any one of claims 1, 3, 17 or 19, wherein said cardiovascular disorder is congestive heart failure.

17. A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a biologically active fragment of a 9q PCIP polypeptide comprising at least 10 amino acid residues of a sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28 or a cell expressing said biologically active fragment of said 9q PCIP polypeptide with a test compound; and

b) determining whether said biologically active fragment binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

18. The method of claim 17, wherein the binding of said test compound to said biologically active fragment of said 9q PCIP polypeptide, is detected by a method selected from the group consisting of:

a) detection of binding by direct detection of test compound/biologically active fragment binding;

b) detection of binding using a competition binding assay; and

c) detection of binding using an assay for PCIP activity.

19. A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a biologically active fragment of a 9q PCIP polypeptide comprising at least 10 amino acid residues of a sequence selected from the group consisting of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, and 28, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said biologically active fragment of said 9q PCIP polypeptide, thereby identifying a compound suitable for treating a cardiovascular disorder.

20. The method of any one of claims 17, 18, or 19, wherein said biologically active fragment of a 9q PCIP polypeptide comprises an EF domain.

21. The method of any one of claims 17, 18 or 19, wherein said biologically active fragment of a 9q PCIP polypeptide comprises amino acid residues 68-252 of human 9q.

23. The method of any one of claims 17, 18, or 19, wherein said biologically active fragment of a 9q PCIP polypeptide comprises a Kv4.3 or Kv4.2 potassium channel α subunit binding domain.

24. The method of claim 20, wherein the EF domain is selected from the group consisting of:

a) residues 116-127, 153-164, 189-200, or 237-248 of SEQ ID NO:14;

b) residues 103-114, 140-151, 176-187, or 224-235 of SEQ ID NO:16;

c) residues 116-127, 153-164, 189-200, or 237-248 of SEQ ID NO:18;

d) residues 98-109, 135-146, 171-182, or 219-230 of SEQ ID NO:20;

e) residues 98-109, 135-146, 171-182, or 219-230 of SEQ ID NO:22;

f) residues 116-127, 103-114, 139-150, or 187-198 of SEQ ID NO:24;

g) residues 66-77, 103-114, 189-200 or 237-248 of SEQ ID NO:26; and

h) residues 98-109, 135-146, 171-182, or 219-230 of SEQ ID NO:28.